



**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re application of

Hiroaki TAKAYAMA, et al.

Appln. No.: 09/214,155

Group Art Unit: 1616

Confirmation No.: 5866

Examiner: Sabiha N. Qazi

Filed: December 29, 1998

For: VITAMIN D3 DERIVATIVE AND ITS PRODUCTION METHOD

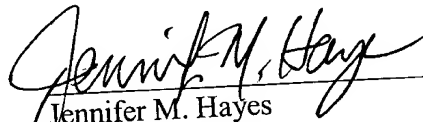
**SUBMISSION OF APPELLANT'S BRIEF ON APPEAL**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

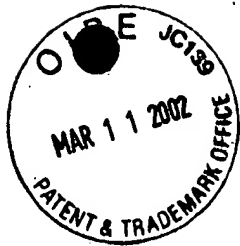
Submitted herewith please find an original and two copies of Appellant's Brief on Appeal. A check for the statutory fee of \$320.00 is attached. Authorization is also given to charge or credit any difference or overpayment to Deposit Account No. 19-4880. A duplicate copy of this paper is attached.

Respectfully submitted,

  
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Date: March 11, 2002



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For: VITAMIN D3 DERIVATIVE AND ITS PRODUCTION METHOD

**APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellant submits the following:

**I. REAL PARTY IN INTEREST**

The real party in interest is TEIJIN LIMITED, a Japanese body corporate.

**II. RELATED APPEALS AND INTERFERENCES**

There are no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**III. STATUS OF CLAIMS**

**A. Claims Appealed**

Appellants carry forward this appeal with respect to claims 3 and 4.

**B. Status of all Claims**

APPELLANTS' BRIEF ON APPEAL  
UNDER 37 C.F.R. § 1.192  
U.S. Appl. No. 09/214,155

Claims 1 and 2 were cancelled in an Amendment filed on August 1, 2000.

**IV. STATUS OF AMENDMENTS**

A Response Under 37 C.F.R. § 1.116 was filed on November 13, 2001, along with a Declaration under 37 C.F.R. § 1.132. In an Advisory Action mailed on November 26, 2001, the Examiner indicated that the double patenting rejection of claims 3 and 4 would be withdrawn upon the abandonment of copending application no. 09/068,219. Further, the Declaration was made of record and considered but found not to be persuasive.

**V. SUMMARY OF THE INVENTION**

The present invention relates to the 20(S) form of 1,25-dihydroxy-2-methylvitamin D<sub>3</sub> derivatives which are useful as agents for treating osteoporosis and their production methods. (Page 1, lines 8-10).

Claim 3 is directed to specifically recited 20(S) form of 1,25-dihydroxy-2-methylvitamin D<sub>3</sub> derivatives which exhibit unexpectedly superior effects over the prior art 20(R) vitamin D<sub>3</sub> derivative compounds as shown in the table on page 39 and in the declarations submitted on December 30, 1999 and November 13, 2001, i.e., compound 68, (Example 2, page 33 of the specification); compound 74 (Example 5, page 36 of the specification); compound 74 (Example 7, page 32 of the specification); and compound 72 (Example 1, page 32 of the specification).

Claim 4 is directed to a method of making the same specifically recited compounds.

## **VI. ISSUES**

The essential issue in the present appeal is whether Applicants have provided sufficient evidence establishing unexpectedly superior properties of the specifically recited compounds when compared to the closest prior art example.

## **VII. GROUPING OF CLAIMS**

All claims stand or fall together.

## **VIII. ARGUMENTS**

Claim 3 is rejected over Miyamoto et al (US Patent No. 5,877,168). The Examiner asserts that the claimed compounds are structurally similar isomers of the compounds disclosed by Miyamoto et al which are known to have calcium regulatory activity and differentiation stimulating activity on tumor cells, etc., and are useful as treating agents for diseases caused by abnormal calcium, such as osteoporosis and osteomalacia, or as an antitumor agent. It is the Examiner's position that the structurally related compounds suggest each other and would be expected to share common properties absent a showing of unexpected results.

A rejection based upon structural similarity of compounds may be rebutted by a showing of unexpectedly superior properties of the claimed compounds over the prior art. *In re Weichert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967). Further it has been established that evidence of unobviousness or unexpected advantageous properties, including superiority of a property of the claimed compound where the prior art compound is known to possess the same or similar properties is sufficient to rebut a prima facie case of obviousness. *See, In re Chupp* 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)(where showing that claimed herbicide was

APPELLANTS' BRIEF ON APPEAL

UNDER 37 C.F.R. § 1.192

U.S. Appln. No. 09/214,155

more effective than the closest prior art compound was held to be sufficient to overcome rejection under 35 U.S.C. § 103); *Ex Parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpectedly superior therapeutic activity of the claimed compound was sufficient to rebut *prima facie* case of obviousness).

In the present case, Applicants have provided evidence of unexpectedly superior properties of the specifically claimed 20(S) vitamin D<sub>3</sub> vitamin derivative compounds, i.e.,

- (i) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (ii) (20S)-1  $\beta$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\alpha$  -vitamin D<sub>3</sub>;
- (iii) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (iv) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\alpha$  -vitamin D<sub>3</sub>,

in the specification on page 39 and in the Declarations under 37 C.F.R. § 1.132 submitted December 30, 1999, (the executed declaration was filed on August 1, 2000) and on November 13, 2001. The data provided clearly establishes unexpectedly superior properties of the specifically claimed 20(S) vitamin D<sub>3</sub> derivatives when compared to 20(R) vitamin D<sub>3</sub> derivative compounds such as those disclosed by Miyamoto et al, which are the closest prior art compounds as stereoisomers of the claimed 20(S) compounds. Specifically, the Declaration filed on November 13, 2001, shows the results from a comparison of the activity of 20(S) compounds of the claimed invention at concentrations ranging from  $1 \times 10^{-12}$  M to  $1 \times 10^{-9}$  M to the activity of 20(R) compounds at concentrations ranging from  $1 \times 10^{-10}$  M to  $1 \times 10^{-7}$  M. Additionally, the claimed compounds are compared to the closest prior art compounds at the same concentration in a side by side comparison and unexpectedly superior results were obtained, i.e., 20(S) form is

APPELLANTS' BRIEF ON APPEAL  
UNDER 37 C.F.R. § 1.192  
U.S. Appln. No. 09/214,155

compared to the corresponding 20(R) form at concentrations of  $10^{-9}$  and  $10^{-10}$ . The tests establish that the claimed 20(S) form compounds are substantially more potent, i.e., require logarithmically lower concentrations, in their ability to induce cell differentiation.

Thus, Applicants respectfully submit that sufficient evidence of unexpectedly superior results of the specifically recited compounds has been provided. Accordingly, Applicants respectfully request reversal of the obviousness rejection of pending claim 3.

Claim 4 is rejected under 35 U.S.C. § 103 under Trost, et al., (J. Am. Chem. Soc. Vol. 114, pages 9836-45, 1992). According to the Examiner, Trost discloses a palladium-catalyzed alkylative cyclization of enynes for the synthesis of vitamin D derivatives. The Examiner asserts that the difference between the claimed invention and the disclosure of Trost is that in the present invention a different starting material is used wherein the starting compound of the claimed invention has a methyl group at the 4-position of the compound of formula III and Trost discloses an unsubstituted 4-position, but that both are enynes of formula III. Thus, the Examiner concludes that one of ordinary skill in the art would have been motivated to use the process of Trost in order to obtain the instant derivatives since the starting materials would be expected to react similarly.

Applicants respectfully submit that the Examiner has not made a *prima facie* showing of obviousness. To establish a *prima facie* case of obviousness there must be (1) some suggestion or motivation within the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference; (2) a reasonable expectation of success; and (3) the prior art reference must teach or suggest all of the claimed limitations. *See Hodesh v. Block Drug Co.*

APPELLANTS' BRIEF ON APPEAL  
UNDER 37 C.F.R. § 1.192  
U.S. Appln. No. 09/214,155

786 F.2d 1136, 1153, n.5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 1438 (Fed. Cir. 1991); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974.

In this case, there is no teaching or suggestion within the reference to modify the disclosed process such that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed 20(S) vitamin D<sub>3</sub> derivatives, having unexpectedly superior properties as shown and discussed above. Applicants submit that it has been established that where a method for preparing purified isomers of compounds, such as the claimed 20(S) vitamin D<sub>3</sub> derivatives, is not taught or suggested by a reference, then a *prima facie* case of obviousness has not been established. Applicants rely on the holding of *Emory University v. Glaxo Wellcome, Inc.* (44 USPQ2d 1407 (DC NGa 1997)) citing *In re Hoeksema* (158 USPQ 596, (CCPA 1968) for the holding that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public".

In addition, Applicants submit that the Examiner failed to consider the claimed invention as a whole. The reference does not teach all of the limitations of the claimed invention, namely, the specifically recited 20(S) form vitamin D<sub>3</sub> derivative compounds. The fact that the reference may teach a similar process is not sufficient by itself to establish obviousness under the fact intensive inquiry required by 35 U.S.C. § 103. *In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995)(where the Court reversed the Board of Appeals and the Examiner stating that both had used incorrect methodology in determining obviousness of a process for making a

APPELLANTS' BRIEF ON APPEAL

UNDER 37 C.F.R. § 1.192

U.S. Appln. No. 09/214,155

compound based upon a “general obviousness rule that a claim is obvious if prior art references disclose the same general process using similar starting materials” stating that no such *per se* rule exists).

As in the case of *In re Ochiai*, the Examiner's rejection is based upon a general rule of obviousness that a process claim is obvious if the prior art references disclose the same general process using similar starting materials. The Examiner has maintained the position that the starting materials of the claimed invention are analogous to those taught by Trost et al because they are both enynes of formula III. As a basis for the rejection the Examiner states and maintains, “[i]t has been held that application of an old process to a[n] analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill”. However such an analysis does not take into consideration the fact that the compounds of formula III of the claimed invention are different as well as the fact that the recited 20(S) vitamin D<sub>3</sub> derivative compounds are different and have been shown to possess unexpectedly superior properties over the closest prior art compounds.

Further, the compound of claim 4 is an intermediate compound rather than a starting material as incorrectly stated by the Examiner, and the intermediate compound is essential for the claimed process with respect to the preparation of the specific 20(S) form vitamin D recited in the claims. Applicants submit that the data showing unexpectedly superior results of the final product is sufficient to establish the patentability of the claimed process.

APPELLANTS' BRIEF ON APPEAL

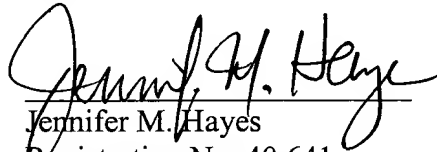
UNDER 37 C.F.R. § 1.192

U.S. Appln. No. 09/214,155

The present Brief on Appeal is being filed in triplicate. Unless a check is submitted herewith for the fee required under 37 C.F.R. §1.192(a) and 1.17(c), please charge said fee to Deposit Account No. 19-4880.

Appellant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

  
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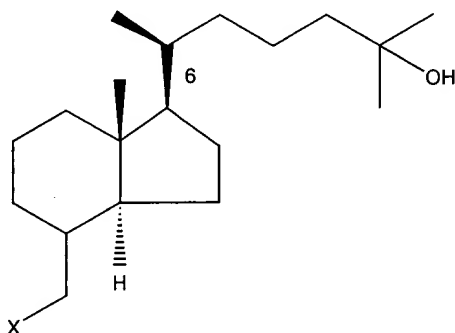
APPENDIX

CLAIMS 3 and 4 ON APPEAL:

Claim 3. A 1,25-dihydroxy-2-methylvitamin D<sub>3</sub> wherein the derivative is

- (i) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (ii) (20S)-1  $\beta$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\alpha$  -vitamin D<sub>3</sub>;
- (iii) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (iv) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\alpha$  -vitamin D<sub>3</sub>.

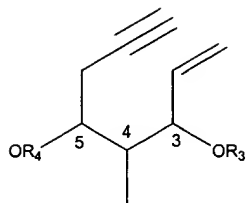
Claim 4. A method for producing a vitamin D<sub>3</sub> derivative described in claim 3,  
comprising reacting an exo-methylene compound of formula (II):



wherein X is a bromine atom or an iodine atom, with an ene-yne compound of formula (III):

Appellants' Brief

U.S. Application Serial No. 09-214,155



wherein R3 and R4 are each independently a hydrogen atom or a tri (C1 to C7 hydrocarbon) silyl) group in the presence of a palladium catalyst, and optionally removing the protecting group of the tri (C1 to C7 hydrocarbon) silyl) group, and further wherein the vitamin D<sub>3</sub> derivative is

- (i) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (ii) (20S)-1  $\beta$ , 25-dihydroxy-2 $\beta$ -methyl-3 $\alpha$  -vitamin D<sub>3</sub>;
- (iii) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\beta$ -vitamin D<sub>3</sub>;
- (iv) (20S)-1 $\alpha$ , 25-dihydroxy-2 $\alpha$  -methyl-3 $\alpha$  -vitamin D<sub>3</sub>.